UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/218,913	12/22/1998	RODERICK L. HALL	98.736	2461

28213 7590 12/02/2005

DLA PIPER RUDNICK GRAY CARY US, LLP
4365 EXECUTIVE DRIVE
SUITE 1100
SAN DIEGO, CA 92121-2133

EXAMINER	
NASHED, NASHAAT T	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 12/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/218,913	HALL ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *11-13, and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,14 and 16-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 3, 2005 has been entered.

The application has been amended as requested n the communication filed October 3, 2005. Accordingly, claims 1 and 19 have been amended; and new claim 30 has been added.

Claims 1-10, 14, and 16-30 are under consideration as they pertain to SEQ ID NO: 52.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-10, 14, and 16-29 are rejected under 35 U.S.C. 102(e) as being anticipated by U. S. Patent 6,583,108 (Tamburini *et al*).

The '108 patent teaches the human bikunin of SEQ ID NO: 52, see the bottom of column 2. The human bikunin of SEQ ID NO: 52 is identical to that of SEQ ID NO: 52 of the instant application, and its use in the treatment of emphysema, an obstructive lung disease (COLD), (claims 1, 14, and 16-19), see column 15, second paragraph. The '108 patent teach the formulation of the human bikunin into a pharmaceutical composition including aerosol and dry powder inhaler (claims 2-10 and 20-28), see from the second paragraph at column 20 through line 25 of column 21. In addition, the patent teaches the expression of SEQ ID NO: 52 in SF9 cells and characterization of a soluble placental bikunin which is glycosylated (claim 29), see example 9, starting at the bottom of column 45.

In response to the above rejection, applicants argue that the reference teach the treatment of ARAD which is not is not COLD, and that the reference is not enabling for the claimed invention.

Applicants' arguments filed 10/3/05 have been fully considered, but they are found unpersuasive. The examiner agrees that ARAD is not COLD, but the '108 patent teaches specifically the use of the human bikunin of SEQ ID NO: 52 for the treatment of emphysema, an obstructive lung disease (COLD), (claims 1, 14, and 16-19), see column 15, second paragraph. While the '108 patent does not use the phrase "accelerating the rate of mucociliary clearance", carrying the therapeutic method described in '108 patent will result in "accelerating the rate of mucociliary clearance". The '108 patent is fully enabling disclosure for making the pharmaceutical composition containing the human bikunin and its use for treatment of emphysema. Thus, the reference anticipates the claimed invention. Since a single reference anticipate the claimed invention, the rejection remains proper

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1-10, 13, and 16-30 are rejected under 35 U.S.C. 103 as being unpatentable over Delaria *et al.* (J. Biol. Chem. 1997, 272 (18), 12209-12214) in view of

the state of the art as exemplified by Rasche *et al.* [IDS, paper number 16, reference number 7, *Medizinische Klinik*, 72 (5), 145-160 (1975), see English translation filed 1/9/03], Fritz *et al.* (U. S. Patent 5,407,915), O'Riordan *et al.* (IDS: Am. J. Respir. Crit. Care Med Vol. 155, pp. 1522-1528), and WO9309233 ('233).

Delaria *et al.* teach the expression in SF9 cells and characterization of a soluble placental bikunin, having N-terminus sequence ADRER- and 170 amino acid residues corresponding to SEQ ID NO: 52 of the instant application, see the abstract and page 12211, the first two paragraph of the result section. Also, they teach the 170 amino acid residue protein contains two Kunitz-type domains corresponding to residues 7-64 and 102-159. Table 1 on page 12213 shows the inhibition constants for bikunin of SEQ ID NO: 52, two polypeptide corresponding to the two Kunitz domains of bikunin, and aprotinin inhibition of various serine proteases. The results indicate that bikunin and its Kunitz fragments are potent inhibitors of serine proteases. It should be noted that bikunin1-170 is expressed in SF9 insect cells, and therefor is expected to be glycosylated. Delaria *et al.* do not teach the use of bikunin1-170 in the treatment of any diseases or conditions.

Rasche *et al.* teach the use of aprotonin, a Kunitz-type serine protease inhibitor, isolated from bovine organs and formulated in a commercially available pharmaceutical composition known as TRASYLOL in the treatment of chronic obstructive bronchitis. TRASYLOL inhibits the symptoms of the disease and is well tolerated by patents; see English version filed 1/9/03, the abstract, and page 8, second and third paragraph. Also, they teach the administration of aprotinin by inhalation to the lungs; see the first paragraph at page 2.

Fritz *et al.* teach the desirability of low molecular weight human protein having a Kunitz-type domain for the treatment of diseases related to excess activity of neutrophil elastase such as emphysema which is an obstructive lung disease (COLD), also known as obstructive pulmonary disease (COPD); see column 1, lines 24-62. They teach a human inter-α-trypsin inhibitor ITI (bikunin) that differs from the bikunin of the instant application. Said inhibitor contains two Kunitz domain corresponding to residues 22-77 and 78-147 each of which is capable of inhibiting serine proteases, see the paragraph bridging column 1 and 2. Also, they teach various analogs of bikunin and its Kunitz domains that are specific inhibitors, see examples 1-5, and the formulation of the inhibitors into pharmaceutical compositions, see from column 4, line 37 through column 6, line 48, in particular column 5, lines 40-46.

O'Riordan *et al.* teach that antigen-induced bronco constriction is associated with impairment of mucociliary clearance, and the contribution of neutrophil elastase to the development to the development of such a condition, see the first paragraph after the abstract.

WO9309233 ('233) patent document teach the use of Kunitz type serine protease inhibitor for the treatment of cystic fibrosis; see pages 29, lines 3-7, and 32, third paragraph. Similar to other COLD related diseases, cystic fibroses is know to be related to excess serine protease activities.

Rasche *et al.* provide one of ordinary skill in the art with motivation and expectation of success to develop a method for treatment of a COPD such as in the case of chronic obstructive bronchitis using composition of Kunitz-type inhibitor. Fritz *et al.* motivate one of ordinary skill in the art to use human proteins having low molecular weigh such as bikunin. Delaria *et al.* provide one of ordinary skill in the art with motivation to use the human placental bikunin expressed in mammalian cells in the pharmaceutical composition as they teach a water-soluble glycosylated human bikunin. The ordinary skill in the art would have been further motivated to use a glycosylated human protein to avoid the development of immune reaction, in particular, in situation where chronic treatment is required such as in COLD related diseases. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to formulate the glycosylated human protein of SEQ ID NO: 52 taught by Delaria *et al.* in a pharmaceutical composition by well known methods in the art such as those taught by Fritz *et al.*; and use the composition in a method to treat a COPD condition taught by Rasche *et al.* (claims 1-3, 14, 16, 19-21, and 29). Also, it would have been further obvious to treat cystic fibroses, a COLD disease with said composition, which is taught by '233 patent document (claim 30). It should be noted that one of ordinary skill in the art would have been able to prepared several aersolizable compositions such as dry powder, suspensions, or solutions of SEQ ID NO: 52 and use them for the treatment of indicated conditions by the administration of the composition directly to the lungs air ways taught by Rasche *et al.* (claims 4-10, and 22-28), see for example Fritz *et al.*, from last paragraph of column 4 through to line 48 of column 6. Also, it should be noted all the cystine residues cited in claim 18 are found in SEQ ID NO: 52, and therefore, the protein is expected to form the requisite disulfide bonds (claims 17 and 18). Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

In response to the above rejection, applicants argue that the combinations of the references are improper becuase: (a) the prior art must contain all the limitation of the claims, (b) the examiner applies the benefit of hindsight sight, and (c) ARAD is not COLD.

Applicants' arguments filed 10/3/05 have been fully considered, but they are found unpersuasive. Thirty years ago, Rasche *et al.* have used commercial preparation of aprotinin, a well-known Kunitz serine protease inhibitor from beef, named TRASYLOL for the treatment of chronic obstructive bronchitis (COLD), a chronic obstructive lung disease. They reported that the inhalation treatment produced an impressive drop in the avarage airway resistance, see page of the translated document filed 1/9/03 at page 8, second paragraph. The difference between the teachings of Rasche *et al.* and the

claimed invention is the source of the protein used in the treatment and its structure. The prior art provide teaching and motivation to one of ordinary skill in the art to use fragments of the human bikunin corresponding to one of the two Kunitz domains in glycosylated form, see Delaria *et al.* and Fritz *et al.* Thus, the prior art provide the motivation, the expectation of success, and the teaching of how to make the composition and its use for the treatment COLD.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Although the examiner agrees that ARAD is not COLD, the claims remain clearly *prima facie* obvious becuase the cited prior art itself teach the treatment of COLD using Kunitz-type serine protease inhibitor for the treatment of COLD, see in particular the title, and abstract of Rasche *et al.* and Fritz *et al.*, column 1, line 31.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen M. Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

N Shed

Nashaat T. Nashed, Ph. D.
Primary Examiner